

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
8 March 2001 (08.03.2001)

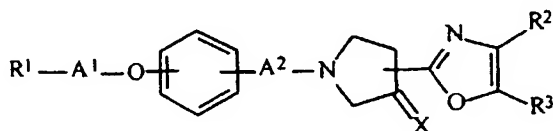
PCT

(10) International Publication Number
WO 01/16132 A1

- (51) International Patent Classification⁷: C07D 413/04, A61K 31/422, A61P 9/08
- (21) International Application Number: PCT/JP00/05453
- (22) International Filing Date: 14 August 2000 (14.08.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
PQ 2531 30 August 1999 (30.08.1999) AU
- (71) Applicant (for all designated States except US): FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): HATTORI, Kouji [JP/JP]; Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). TANAKA, Akira [JP/JP]; Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP).
- (81) Designated States (national): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
— With international search report.
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/16132 A1

(54) Title: 4,5-DIARYLOXAZOLE COMPOUNDS WITH PROSTAGLANDIN 12 (PG12) AGONISTIC ACTIVITY



(I)

(57) Abstract: Heterocyclic compounds of formula (I) wherein R¹ is carboxy or protected carboxy, R² is aryl which may have substituent(s), R³ is aryl which may have substituent(s), X is oxygen or a pair of hydrogen and R⁵ (wherein R⁵ is hydroxy or protected hydroxy), and A¹ and A² are each independently lower alkylene and pharmaceutically acceptable salts thereof which are

useful as a medicament.

DESCRIPTION

4,5-DIARYLOXAZOLE COMPOUNDS WITH PROSTAGLANDIN I₂ (PGI₂) AGONISTIC ACTIVITY

5 TECHNICAL FIELD

This invention relates to new heterocyclic compounds and pharmaceutically acceptable salts thereof which are useful as a medicament.

BACKGROUND ART

10 Some heterocyclic compounds have been known as described, for example, in WO95/17393, WO95/24393, WO97/03973, US-A-5362879 and EP-A-434034.

DISCLOSURE OF INVENTION

15 This invention relates to new heterocyclic compounds. More particularly, this invention relates to new heterocyclic compounds and pharmaceutically acceptable salts thereof which have prostaglandin I₂ (hereinafter referred as PGI₂) agonistic activity and pharmacological activities such as an inhibitory activity on platelet aggregation, vasodilating
20 activity, antihypertensive activity or the like, to processes for their production, to a pharmaceutical composition containing the same and to a use thereof for manufacture of medicaments.

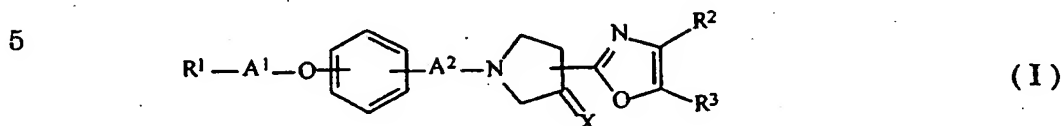
Accordingly, one object of this invention is to provide new and useful heterocyclic compounds and pharmaceutically acceptable salts thereof.

25 Another object of this invention is to provide processes for production of the heterocyclic compounds and salts thereof.

A further object of this invention is to provide a pharmaceutical composition containing, as an active ingredient, said heterocyclic compounds or pharmaceutically acceptable salts thereof.

30 Still further object of this invention is to provide use of the heterocyclic compounds and pharmaceutically acceptable salts thereof for manufacture of medicaments for the therapeutic and/or prophylactic treatment of arterial obstruction, cerebrovascular disease, hepatic cirrhosis, arteriosclerosis, ischemic heart disease, restenosis after percutaneous
35 transluminal coronary angioplasty, hypertension, dermatitis or the like.

The heterocyclic compounds of this invention can be represented by the following formula (I):



wherein R¹ is carboxy or protected carboxy,

R² is aryl which may have substituent(s),

10 R³ is aryl which may have substituent(s),

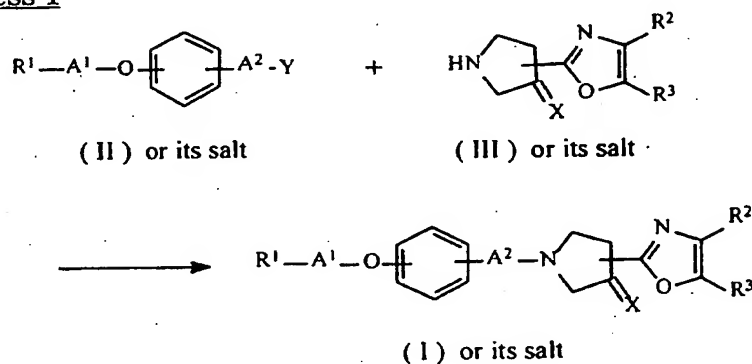
X is oxygen or a pair of hydrogen and R⁵ (wherein R⁵ is hydroxy or protected hydroxy), and

A¹ and A² are each independently lower alkylene and prodrug thereof, and its salt.

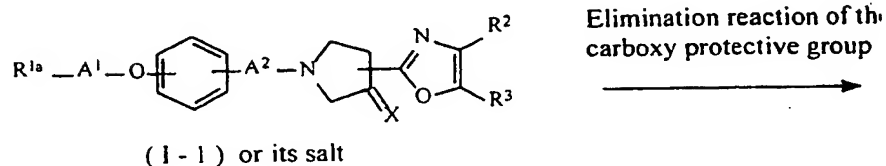
15

According to the present invention, the new heterocyclic compounds (I) can be prepared by the processes which are illustrated in the following scheme.

20 Process 1

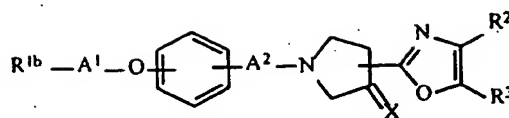


30 Process 2



35

3



(1 - 2) or its salt

5

wherein R^1 , R^2 , R^3 , X , A^1 and A^2 are each as defined above,

Y is leaving group,

R^{1a} is protected carboxy, and

R^{1b} is carboxy.

10

Suitable pharmaceutically acceptable salts of the object compound (I) are conventional non-toxic salts and include a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N' -dibenzylethylenediamine salt, etc.), an organic acid salt (e.g. acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.), and the like.

20

The "prodrug" means the derivatives of compounds of the present invention having a chemically or metabolically degradable group, which becomes pharmaceutically active after biotransformation.

25

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope thereof are explained in detail as follows.

30 The term "lower" is intended to mean 1 to 6 carbon atom(s), unless otherwise indicated.

Suitable "aryl" may include phenyl, naphthyl and the like.

Suitable "lower alkylene" may include straight one having 1 to 6 carbon atom(s), such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene and hexamethylene, preferably one having 1 to 3 carbon

35

atom(s).

Suitable "protected carboxy" may include esterified carboxy and the like. Suitable example of the ester moiety of an esterified carboxy may be the ones such as lower alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, etc.) which may have at least one substituent(s), for example, lower alkanoyloxy(lower)alkyl [e.g. acetoxymethyl, propionyloxymethyl, butyryloxymethyl, valeryloxymethyl, pivaloyloxymethyl, hexanoyloxymethyl, 1(or 2)-acetoxylethyl, 1(or 2 or 3)-acetoxypentyl, 1(or 2 or 3 or 4)-acetoxylhexyl, 1(or 2)-propionyloxyethyl, 1(or 2 or 3)-propionyloxypropyl, 1(or 2)-butyryloxyethyl, 1(or 2)-isobutyryloxyethyl, (1 or 2)-pivaloyloxyethyl, 1(or 2)-hexanoyloxyethyl, isobutyryloxymethyl, 2-ethylbutyryloxymethyl, 3,3-dimethylbutyryloxymethyl, 1(or 2)-pentanoyloxyethyl, etc.], lower alkylsulfonyl(lower)alkyl (e.g. 2-mesyloethyl, etc.), mono(or di or tri)-halo(lower)alkyl (e.g. 2-iodoethyl, 2,2,2-trichloroethyl, etc.), lower alkoxy-carbonyloxy(lower)alkyl (e.g. methoxycarbonyloxymethyl, ethoxycarbonyloxymethyl, 2-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl, 1-isopropoxycarbonyloxyethyl, etc.), phthalidylidene(lower)alkyl, or (5-lower alkyl-2-oxo-1,3-dioxol-4-yl)(lower)alkyl [e.g. (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl, (5-propyl-2-oxo-1,3-dioxol-4-yl)ethyl, etc.]; lower alkenyl (e.g. vinyl, allyl, etc.); lower alkynyl (e.g. ethynyl, propynyl, etc.); ar(lower)alkyl which may have at least one substituent(s) such as mono(or di or tri)phenyl(lower)alkyl which may have at least one substituent(s) (e.g. benzyl, 4-methoxybenzyl, 4-nitrobenzyl, phenethyl, trityl, benzhydryl, bis(methoxyphenyl)methyl, 3,4-dimethoxybenzyl, 4-hydroxy-3,5-di-tert-butylbenzyl, etc.); aryl which may have at least one substituent(s) (e.g. phenyl, 4-chlorophenyl, tolyl, tert-butylphenyl, xylyl, mesityl, cumenyl, etc.); phthalidyl; and the like.

Suitable "substituent" in the term "aryl which may have substituent(s)" may include halogen, amino, hydroxy, lower alkoxy, lower alkyl as exemplified above, and the like.

Suitable "halogen" may include fluoro, chloro, bromo and iodo.

Suitable "lower alkyl" may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, t-pentyl, hexyl or the like, preferably one having 1 to

4 carbon atom(s).

Suitable "lower alkoxy" may include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentyloxy, t-pentyloxy, hexyloxy and the like.

- 5 Suitable "acyl" may include (1) lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, oxalyl, succinyl, pivaloyl, etc.); (2) lower alkanesulfonyl (e.g. mesyl, ethanesulfonyl, propanesulfonyl, isopropanesulfonyl, butanesulfonyl, etc.); (3) arenesulfonyl (e.g. benzenesulfonyl, tosyl, etc.); (4) aroyl (e.g. benzoyl, toluoyl, xyloyl, naphthoyl, phthaloyl, indancarbonyl, etc.); (5) ar(lower)alkanoyl (e.g. phenylacetyl, phenylpropionyl, etc.); and the like.

Suitable "protected hydroxy" may include lower alkoxy as exemplified above, acyloxy, siloxy which may have one to three substituent(s), and the like.

- 15 Suitable "substituent" in the term "siloxy which may have one to three substituent(s)" may include lower alkyl as exemplified above, aryl as exemplified above, and the like.

- Suitable "substituent" in the term "lower alkylene which may have substituent(s)" may include lower alkyl as exemplified above, hydroxy(lower)alkyl (e.g. hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, etc.) and the like.

Suitable "leaving group" may include halogen as exemplified above, acyloxy (e.g. acetyloxy, methanesulfonyloxy), and the like.

- 25 Preferred embodiments of the object compound (I) are as follows:

R^1 is carboxy or protected carboxy (more preferably esterified carboxy, most preferably lower alkoxycarbonyl),

R^2 is aryl which may have lower alkyl (more preferably phenyl or lower alkylphenyl, most preferably phenyl),

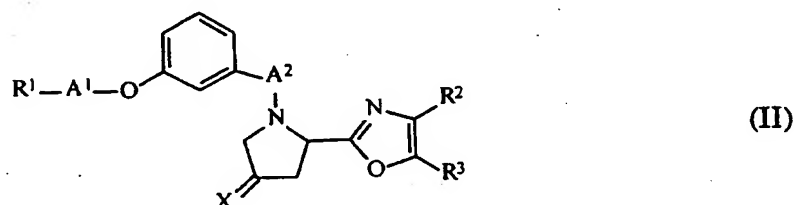
- 30 R^3 is aryl which may have lower alkyl (more preferably phenyl or lower alkylphenyl, most preferably phenyl),

X is oxygen or a pair of hydrogen and R^5 (wherein R^5 is hydroxy or protected hydroxy, more preferably R^5 is lower alkoxy, most preferable R^5 is methoxy), and

- 35 A^1 and A^2 are each independently lower alkylene (more preferably C_1 - C_4

alkylene, most preferably methylene),

Another preferred embodiments of the object compound (I) are as follows:



10 wherein

R¹ is carboxy or lower alkoxycarbonyl (more preferably ethoxycarbonyl),

R² is phenyl or lower alkylphenyl, more preferably phenyl,

R³ is phenyl or lower alkylphenyl, more preferably phenyl,

15 X is oxygen or a pair of hydrogen and R⁵ (wherein R⁵ is hydroxy or lower alkoxy), more preferably a pair of hydrogen and lower alkoxy, most preferably a pair of hydrogen and methoxy, and

A¹ and A² are each independently lower alkylene (more preferably methylene).

20 It is to be noted the object compound (I) may include one or more stereoisomers due to asymmetric carbon atom(s) and double bond, and all of such isomers and a mixture thereof are included within the scope of the present invention.

25 It is further to be noted isomerization or rearrangement of the object compound (I) may occur due to the effect of the light, acid, base or the like, and the compound obtained as the result of said isomerization or rearrangement is also included within the scope of the present invention.

30 It is also to be noted that the solvating form of the compound (I) (e.g. hydrate, etc.) and any form of the crystal of the compound (I) are included within the scope of the present invention.

Also included in the scope of invention are radiorabelled derivatives of the compound of the formula (I) which are suitable for biological studies.

35 The processes for preparing the object and starting compounds of the present invention are explained in detail in the following.

Process 1

The compound (I) or its salt can be prepared by reacting the compound (II) or its salt with the compound (III) or its salt.

5 This reaction is usually carried out in a solvent such as acetonitrile, benzene, N,N-dimethylformamide, tetrahydrofuran, methylene chloride, ethylene chloride, chloroform, diethyl ether or any other solvent which does not adversely affect the reaction.

10 The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

 The reaction is usually carried out in the presence of a base. Suitable base may include the inorganic base such as alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkaline earth metal hydroxide (e.g. magnesium hydroxide, calcium hydroxide, etc.), alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), alkaline earth metal carbonate (e.g. magnesium carbonate, calcium carbonate, etc.) or the like, and the organic base such as tri(lower)alkylamino (e.g., trimethylamine, triethylamine, diisopropylethylamine, etc.), di(lower)alkylaniline (e.g. dimethylaniline, etc.), pyridine or the like.

20

Process 2

 The compound (I-2) or its salt can be prepared by subjecting the compound (I-1) or its salt to elimination reaction of the carboxy protective group. Suitable method of this reaction may include conventional one such as hydrolysis, reduction and the like.

25

(i) For hydrolysis:

 The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

30 Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], the hydroxide or carbonate or bicarbonate thereof, trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

35 Suitable acid may include an organic acid [e.g. formic acid, acetic acid,

propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.]. The elimination using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc.] or the like is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, tetrahydrofuran, 1,2-dimethoxyethane, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

(ii) For reduction:

Reduction is carried out in a conventional manner, including chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of a metal (e.g. tin, zinc, iron, etc.) or metallic compound (e.g. chromium chloride, chromium acetate, etc.) and an organic or inorganic acid (e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, *p*-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.).

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts (e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.), palladium catalysts (e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.), nickel catalysts (e.g. reduced nickel, nickel oxide, Raney nickel, etc.), cobalt catalysts (e.g. reduced cobalt, Raney cobalt, etc.), iron catalysts (e.g. reduced iron, Raney iron, etc.), copper catalysts (e.g. reduced copper, Raney copper, Ullman copper, etc.) and the like. The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, ethyl acetate, N,N-dimethylformamide, tetrahydrofuran, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

The object compound (I) of this invention and pharmaceutically acceptable salt thereof have pharmacological activities such as an inhibitory activity on platelet aggregation, vasodilating activity, antihypertensive activity or the like and are prostaglandin I₂ agonists, and therefore can be used for treating and/or preventing thrombosis, arterial obstruction (e.g., chronic arterial obstruction, etc.), cerebrovascular disease, gastric ulcer, hepatitis, hepatic insufficiency, hepatic cirrhosis, arteriosclerosis, ischemic heart disease, restenosis or ischemic complications after coronary angioplasty (e.g., PTCA, coronary stenting, etc.), hypertension, inflammation, autoimmune disease, heart failure, renal disease (e.g., renal failure, nephritis, etc.), diabetic complication (e.g., diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, etc.), peripheral circulatory disturbance, dermatitis, chilblain, baldness, bed sore, and the like, inflammatory bowel disease (such as specific inflammatory bowel disease [e.g., infectious enteritis, drug induced colitis (e.g., antibiotics associated colitis, etc), ischemic colitis, etc.], idiopathic inflammatory bowel disease (e.g., ulcerative colitis, Crohn's disease, etc) and the like), and the like, and can be also used for protecting organs after transplantation or surgery.

Further, the object compound (I) and pharmaceutically acceptable salt thereof can be also used as a component for organ preserving fluids and as an agent for inhibiting metastasis of cancer.

The object compound (I) was confirmed to have a potent PGI₂ agonistic activity. Further in order to show the inhibitory activity on platelet aggregation, pharmacological data of the representative compounds thereof are shown in the following.

Inhibition of human platelet aggregation induced by ADP

[I] Test Compound:

- (1) Sodium 3-{[(2R,4R)-2-(4,5-diphenyloxazol-2-yl)-4-methoxypyrrolidin-1-yl]methyl}phenoxyacetate
- (2) Sodium 3-{[(2R,4S)-2-(4,5-diphenyloxazol-2-yl)-4-methoxypyrrolidin-

1-yl)methyl]phenoxyacetate

[II] Test Method:

Human blood was obtained from healthy volunteers and mixed with
5 1/10 volume of 3.8% sodium citrate, pH 7.4. The citrate blood was
centrifuged at 150 x g for 10 minutes and the platelet rich plasma (PRP) was
removed. The remaining blood was centrifuged for a further 10 minutes at
1500 x g to prepare the platelet poor plasma (PPP), which was used as a
reference for platelet aggregation. Aggregation studies were carried out
10 using HEMATRACER 801 (NBS, Japan), a 8 channel aggregometer. The
test compound solution (25 µl) and the PRP (225 µl) were mixed and stirred at
1000 rpm at 37°C for 2 minutes. Aggregation was induced by ADP solution
at the final concentration of 2.5 µM.

15 [III] Test Result:

| Test Compound | IC ₅₀ |
|---------------|--------------------------------|
| (1) | $< 1 \times 10^{-7} \text{ M}$ |
| (2) | $< 1 \times 10^{-7} \text{ M}$ |

The active ingredient of this invention can be used in a form of a
pharmaceutical preparation, for example, in solid, semisolid or liquid form,
20 which contains a compound (I), as an active ingredient, in admixture with an
organic or inorganic carrier or excipient suitable for external, enteral,
intravenous, intramuscular, parenteral or intramucous applications. The
active ingredient may be compounded, for example, with the conventional
non-toxic, pharmaceutically acceptable carriers for ointment, cream, plaster,
25 tablets, pellets, capsules, suppositories, solution (saline, for example),
emulsion, suspension (olive oil, for example), aerosols, pills, powders, syrups,
injections, troches, cataplasms, aromatic waters, lotions, buccal tablets,
sublingual tablets, nasal drops and any other form suitable for use. The
carriers which can be used are water, wax, glucose, lactose, gum acacia,
30 gelatin, mannitol, starch paster, magnesium trisilicate, talc, corn starch,

keratin, paraffin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The active compound is included in a pharmaceutical composition in an effective amount sufficient to produce the desired effect upon the process or condition of the diseases.

The active ingredient may be compounded into, for example, preparations for oral application, preparations for injection, preparations for external application, preparations for inhalation, preparations for application to mucous membranes

The effective ingredient may usually be administered with a unit dose of 0.01 mg/kg to 50 mg/kg, 1 to 4 times a day. However, the above dosage may be increased or decreased according to age, weight, and conditions of the patient or the administering method.

The compound (I) of the present invention has much advantage, such as more selective PGI₂ antagonistic activity, stronger activity, more suitable half-life, decreased adverse effect, or the like, compared to the known heterocyclic compounds having the PGI₂ antagonistic activity.

The patents, patent applications and publications cited herein above are incorporated by reference.

Abbreviations used in this application are as follows:

| | | |
|----------------------|---|--|
| THF | : | Tetrahydrofuran |
| EtOAc | : | Ethyl acetate |
| 25 DMSO | : | Dimethyl sulfoxide |
| DMF | : | N,N-Dimethylformamide |
| TBDMSCl | : | <i>tert</i> -Butyldimethylsilyl chloride |
| EtOH | : | Ethyl alcohol |
| MeOH | : | Methyl alcohol |
| 30 Et ₂ O | : | Diethyl ether |
| AcONH ₄ | : | Ammonium acetate |
| AcOH | : | Acetic acid |
| MeCN | : | Acetonitrile |

The following Preparations and Examples are given only for the purpose of illustrating the present invention in more detail.

Preparation 1

- 5 A suspension of *cis*-4-hydroxy-D-proline (10.0 g) in THF-water (1:1, 100 mL) was added 1N NaOH solution (50 mL) at 5°C. To the mixture was added a solution of benzyloxycarbonyl chloride (12.5 mL) in THF (10 mL) keeping pH to 8.5-10 by the addition of 2N NaOH solution at 5-10°C. After stirring at the same temperature for 1 h, the reaction mixture was washed with EtOAc (50 mL), adjusted to pH 2 by the addition of 4N HCl, and extracted with EtOAc. The organic layer was washed with water and brine, dried (MgSO₄), and evaporated *in vacuo* to give *cis*-4-hydroxy-N-benzyloxycarbonyl-D-proline (18.74 g).

IR (neat): 3433, 2952, 1680, 1427, 1358, 1209 cm⁻¹

- 15 NMR (DMSO-d₆, δ): 1.80-2.03 (1H, m), 2.21-2.45 (1H, m), 3.14-3.30 (1H, m), 3.50-3.66 (1H, m), 4.13-4.35 (2H, m), 4.96-5.15 (2H, m), 7.20-7.45 (5H, m)

ESI-MS *m/z*: 288 (M+Na⁺)

20 Preparation 2

- To a mixture of *cis*-4-hydroxy-N-benzyloxycarbonyl-D-proline (18.74 g) and imidazole (11.56 g) in DMF (100 mL) was added TBDMSCl (23.36 g) at 5°C. After stirring at room temperature for 16 hours, the reaction mixture was diluted with EtOAc-hexane (1:1, 600 mL), washed with 1N HCl, water and brine, dried (MgSO₄), and evaporated *in vacuo*. The residue was dissolved in MeOH-THF (3:1, 400 mL). To the solution was added an aqueous solution (100 mL) of K₂CO₃ (9.77 g) at 5°C, and the mixture was stirred at the same temperature for 1 hour. The organic solvent was evaporated, and the residue was adjusted to pH 2 by the addition of 3N HCl, and extracted with EtOAc. The organic layer was washed with water and brine, dried (MgSO₄), and evaporated *in vacuo*. The residue was purified by silica gel column chromatography to give *cis*-4-(tert-butyldimethylsilyloxy)-N-benzyloxycarbonyl-D-proline (23.99 g).

IR (neat): 3433, 2952, 1680, 1427, 1358, 1209 cm⁻¹

- 35 NMR (DMSO-d₆, δ): 0.03 and 0.04 (total 6H, each s), 0.80 and 0.81 (total

9H, each s), 1.80-2.00 (1H, m), 2.22-2.45 (1H, m), 3.10-3.22 (1H, m),
3.50-3.68 (1H, m), 4.17-4.45 (2H, m), 4.94-5.13 (2H, m), 7.21-7.40 (5H, m)
Negative ESI-MS m/z : 378 (M-H)⁻

5 Preparation 3

To a mixture of *cis*-4-(tert-butyldimethylsilyloxy)-N-benzyloxycarbonyl-D-proline (21.87 g), benzoin (12.25 g), and 4-dimethylaminopyridine (7.04 g) in CH_2Cl_2 (200 mL) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (10.52 mL) at 5°C, and the mixture was stirred at room temperature for 20
10 hours. The reaction mixture was evaporated, and the residue was dissolved in EtOAc (250 mL), washed with 1N HCl (150 mL), water, saturated sodium hydrogen carbonate solution, water and brine, dried (MgSO_4), and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-EtOAc, 5:2 elution) to give *cis*-4-(tert-butyldimethylsilyloxy)-N-
15 benzyloxycarbonyl-D-proline 2-oxo-1,2-diphenylethyl ester (21.62 g).
IR (neat) : 3469, 3064, 2952, 2856, 1757, 1707, 1597, 1496, 1450, 1417, 1356 cm^{-1}
NMR ($\text{DMSO}-d_6$, δ) : 0.00-0.15 (6H, m), 0.80-0.93 (9H, m), 1.98-2.27 (1H, m), 2.40-2.73 (1H, m), 3.15-3.30 (1H, m), 3.60-3.83 (1H, m), 4.42-4.75 (2H, 20 m), 5.05-5.19 (2H, m), 6.05-6.17 (1H, m), 6.98-8.15 (15H, m)
ESI-MS m/z : 596 (M+Na⁺)

Preparation 4

To a solution of *cis*-4-(tert-butyldimethylsilyloxy)-N-benzyloxycarbonyl-D-
25 proline 2-oxo-1,2-diphenylethyl ester (21.62 g) in MeOH-THF (2:1, 380 mL) was added 1N HCl (76 mL) at 5°C, and the mixture was stirred at room temperature for 24 hours. To the reaction mixture was added NaHCO_3 (6.7 g) at 5°C. The organic solvent was evaporated, and the residue was extracted with EtOAc. The organic layer was washed with water and brine, dried
30 (MgSO_4), and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-EtOAc, 2:1~1:3 elution) to give *cis*-4-hydroxy-N-benzyloxycarbonyl-D-proline 2-oxo-1,2-diphenylethyl ester (13.90 g).
IR (KBr) : 3465, 3062, 2951, 1755, 1695, 1597, 1417, 1354 cm^{-1}
35 NMR ($\text{DMSO}-d_6$, δ) : 1.94-2.19 (1H, m), 2.30-2.65 (1H, m), 3.08-3.27 (1H, m),

3.50-3.74 (1H, m), 4.17-4.65 (2H, m), 4.94-5.16 (3H, m), 7.05-7.70 (13H, m), 7.99-8.13 (2H, m)

ESI-MS m/z : 482 ($M+Na^+$)

5 Preparation 5

A mixture of *cis*-4-hydroxy-N-benzylloxycarbonyl-D-proline 2-oxo-1,2-diphenylethyl ester (7.0 g) and $AcONH_4$ (11.8 g) in AcOH was stirred at 120°C for 1 hour. The reaction mixture was evaporated, and the residue was dissolved in EtOAc, washed with water, 3N NaOH solution, water and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by silica gal column chromatography (hexane-EtOAc, 1:1~2:3 elution) to give first benzyl (2R, 4R)-4-acetoxy-2-(4,5-diphenyloxazol-2-yl)pyrrolidine-1-carboxylate (972.6 mg), then benzyl (2R, 4R)-2-(4,5-diphenyloxazol-2-yl)-4-hydroxypyrrolidine-1-carboxylate (5.12 g).

15

Benzyl (2R, 4R)-2-(4,5-diphenyloxazol-2-yl)-4-hydroxypyrrolidine-1-carboxylate

IR (neat): 3367, 3060, 2951, 1707, 1446, 1414, 1356, 1209 cm^{-1}

NMR ($CDCl_3$, δ): 2.33-2.63 (2H, m), 3.68-3.93 (2H, m), 4.45-4.61 (1H, m),

20 4.98-5.28 (3H, m), 5.90-6.10 (1H, m), 7.08-7.70 (15H, m)

APCI-MS m/z : 441 ($M+H^+$)

Benzyl (2R, 4R)-4-acetoxy-2-(4,5-diphenyloxazol-2-yl)pyrrolidine-1-carboxylate

25 IR (neat): 3060, 3033, 2951, 1739, 1711, 1500, 1446, 1414, 1354 cm^{-1}

NMR ($CDCl_3$, δ): 1.85 (3H, s), 2.55-2.73 (2H, m), 3.72-4.03 (2H, m), 4.97-5.40 (4H, m), 7.05-7.70 (15H, m)

APCI-MS m/z : 483 ($M+H^+$)

30 Preparation 6

To a solution of benzyl (2R, 4R)-2-(4,5-diphenyloxazol-2-yl)-4-hydroxypyrrolidine-1-carboxylate (350 mg) in MeOH (15 mL) was added 10%Pd-C (wet) (50 mg), and the mixture was stirred under hydrogen atmosphere at room temperature for 1 hour. The catalyst was removed by filtration and the filtrate was evaporated to give (2R, 4R)-2-(4,5-

35

15

diphenyloxazol-2-yl)pyrrolidin-4-ol (236.8 mg).

IR (neat): 3319, 3059, 2941, 1589, 1568, 1502, 1444, 1217, 1061 cm^{-1}

NMR (CDCl_3 , δ): 2.25-2.53 (2H, m), 3.14-3.28 (1H, m), 3.27 (1H, dd, $J = 11.7, 4.5$ Hz), 4.45-4.57 (2H, m), 7.25-7.45 (6H, m), 7.50-7.70 (4H, m)

5 APCI-MS m/z : 307 ($M+H^+$)

Preparation 7

The following compounds (1) to (3) were obtained according to the similar manner to that of preparation 6.

10 (1) (2R, 4S)-2-(4,5-Diphenyloxazol-2-yl)pyrrolidin-4-ol

IR (KBr): 3280, 3145, 2883, 1603, 1566, 1444, 1329, 1221, 1061 cm^{-1}

NMR (CDCl_3 , δ): 2.20-2.38 (1H, m), 2.38-2.55 (1H, m), 3.00-3.12 (1H, m), 3.30 (1H, dd, $J = 11.6, 4.2$ Hz), 4.55-4.68 (1H, m), 4.69 (1H, dd, $J = 7.6, 7.6$ Hz), 7.25-7.45 (6H, m), 7.50-7.70 (4H, m)

15 APCI-MS m/z : 307 ($M+H^+$)

(2) 2-[(2R, 4R)-4-Methoxypyrrolidin-2-yl]-4,5-diphenyloxazole

IR (neat): 3319, 3059, 2929, 2823, 1604, 1568, 1502, 1444, 1358, 1219 cm^{-1}

20 NMR (CDCl_3 , δ): 2.18-2.34 (1H, m), 2.42-2.57 (1H, m), 3.02-3.12 (1H, dd, $J = 11.8, 5.0$ Hz), 3.25-3.35 (1H, m), 3.32 (3H, s), 3.99-4.10 (1H, m), 4.37 (1H, dd, $J = 8.4, 6.8$ Hz), 7.25-7.43 (6H, m), 7.51-7.70 (4H, m)

APCI-MS m/z : 321 ($M+H^+$)

25 (3) 2-[(2R, 4S)-4-Methoxypyrrolidin-2-yl]-4,5-diphenyloxazole

IR (neat): 3330, 3057, 2929, 2823, 1604, 1568, 1502, 1444, 1356, 1219 cm^{-1}

NMR (CDCl_3 , δ): 2.32-2.42 (2H, m), 3.07-3.30 (2H, m), 3.35 (3H, s), 4.04-4.15 (1H, m), 4.61 (1H, dd, $J = 7.6, 7.6$ Hz), 7.25-7.45 (6H, m), 7.50-7.68 (4H, m)

30

APCI-MS m/z : 321 ($M+H^+$)

Preparation 8

To a mixture of benzyl (2R, 4R)-2-(4,5-diphenyloxazol-2-yl)-4-

35 hydroxypyrrolidine-1-carboxylate (1.50 g) and triphenylphosphine (1.43 g) in

THF (15 mL) was added diethyl azodicarboxylate (0.86 mL) at 5°C, and the mixture was stirred at the same temperature for 30 minutes. To the mixture was added AcOH (0.29 mL) at 5°C, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was evaporated, and the residue was dissolved in EtOAc, washed with saturated sodium hydrogen carbonate solution, water and brine, dried (MgSO₄), and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-EtOAc, 2:1 elution) to give benzyl (2R, 4S)-4-acetoxy-2-(4,5-diphenyloxazol-2-yl)pyrrolidine-1-carboxylate (1.88 g).

10 IR (neat): 2983, 1743, 1712, 1500, 1446, 1415, 1358 cm⁻¹
NMR (CDCl₃, δ): 2.09 (3H, s), 2.50-2.63 (2H, m), 3.70-4.03 (2H, m), 4.90-5.35 (3H, m), 5.38-5.50 (1H, m), 7.02-7.70 (15H, m)
APCI-MS m/z: 483 (M+H⁺)

15 Preparation 9

To a solution of benzyl (2R, 4S)-4-acetoxy-2-(4,5-diphenyloxazol-2-yl)pyrrolidine-1-carboxylate (1.49 g) in MeCN (15 mL) was added 28% sodium methylate in MeOH (0.72 mL) at 5°C, and the mixture was stirred at the same temperature for 30 minutes. To the reaction mixture was added 1N HCl (3.8 mL) under ice-cooling, and extracted with EtOAc. The organic layer was washed with water, saturated sodium hydrogen carbonate solution, water and brine, dried (MgSO₄), and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-EtOAc, 1:3 elution) to give benzyl (2R, 4S)-2-(4,5-diphenyloxazol-2-yl)-4-hydroxypyrrolidine-1-carboxylate (980.8 mg).

20 IR (neat): 3433, 3060, 2949, 1707, 1500, 1446, 1417, 1356 cm⁻¹
NMR (CDCl₃, δ): 2.37-2.53 (2H, m), 3.60-3.92 (2H, m), 4.60-4.74 (1H, m), 4.87-5.35 (3H, m), 7.00-7.70 (15H, m)
APCI-MS m/z: 441 (M+H⁺)

30

Preparation 10

To a solution of benzyl (2R, 4R)-2-(4,5-diphenyloxazol-2-yl)-4-hydroxypyrrolidine-1-carboxylate (400 mg) and CH₃I (0.57 mL) in DMF (5 mL) was added NaH (60% oil suspension, 48 mg) at 5°C. The mixture was stirred at the same temperature for 10 minutes, then stirred at room

35

temperature for 30 minutes. The reaction mixture was poured into diluted HCl, and extracted with EtOAc. The organic layer was washed with water, saturated sodium hydrogen carbonate, water and brine, dried (MgSO₄), and evaporated *in vacuo*. The residue was purified by silica gel column

5 chromatography (hexane-EtOAc, 1:1 elution) to give benzyl (2R, 4R)-2-(4,5-diphenyloxazol-2-yl)-4-methoxypyrrolidine-1-carboxylate (402.9 mg).

IR (neat) : 3062, 2943, 1709, 1444, 1414, 1354, 1213, 1095 cm⁻¹

NMR (CDCl₃, δ) : 2.45-2.65 (2H, m), 3.30 (3H, s), 3.60-4.18 (3H, m), 4.93-5.32 (3H, m), 7.02-7.75 (15H, m)

10 APCI-MS m/z : 455 (M+H⁺)

Preparation 11

The following compound was obtained according to the similar manner to that of preparation 10.

15

Benzyl (2R, 4S)-2-(4,5-diphenyloxazol-2-yl)-4-methoxypyrrolidine-1-carboxylate

IR (neat) : 3060, 2939, 1711, 1446, 1414, 1354, 1117, 1095 cm⁻¹

NMR (CDCl₃, δ) : 2.35-2.61 (2H, m), 3.37 (3H, s), 3.65-3.94 (2H, m), 4.09-4.23 (1H, m), 4.87-5.28 (3H, m), 7.00-7.68 (15H, m)

20

APCI-MS m/z : 455 (M+H⁺)

Example 1

To a mixture of (2R, 4R)-2-(4,5-diphenyloxazol-2-yl)pyrrolidin-4-ol (229 mg) and potassium carbonate (155 mg) in DMF (5 mL) was added ethyl 3-(bromomethyl)phenoxyacetate (245 mg) at 5°C and stirred at the same temperature for 30 minutes then at room temperature for 16 hours. The reaction mixture was diluted with EtOAc, washed with water and brine, dried (MgSO₄), and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-EtOAc, 1:2) to give ethyl 3-[(2R, 4R)-2-(4,5-diphenyloxazol-2-yl)-4-hydroxypyrrolidin-1-yl]methyl]phenoxyacetate (359.7 mg).

25

30

IR (neat) : 3386, 3057, 2979, 2804, 1759, 1601, 1591, 1487, 1444 cm⁻¹

NMR (CDCl₃, δ) : 1.27 (3H, t, J = 7.1 Hz), 2.15-2.32 (1H, m), 2.45-2.68

35

(1H, m), 2.87-3.02 (2H, m), 3.60-3.85 (2H, m), 4.04 (1H, dd, J = 8.7, 3.3

Hz), 4.23 (2H, q, J = 7.1 Hz), 4.30-4.55 (1H, m), 4.50 (2H, s), 6.65-6.79 (1H, m), 6.82-7.00 (2H, m), 7.05-7.45 (7H, m), 7.45-7.68 (4H, m)
APCI-MS m/z : 499 (M+H⁺)

5 Example 2

The following compounds (1) to (3) were obtained according to a similar manner to that of example 1.

(1) Ethyl 3-[(2R, 4S)-2-(4,5-diphenyloxazol-2-yl)-4-hydroxypyrrolidin-1-yl]methyl]phenoxyacetate
10 IR (neat) : 3384, 3057, 2979, 2925, 2814, 1759, 1601, 1591, 1487, 1444 cm⁻¹
NMR (CDCl₃, δ) : 1.27 (3H, t, J = 7.1 Hz), 1.78 (1H, d, J = 5.1 Hz), 2.15-2.30 (1H, m), 2.47-2.72 (2H, m), 3.46 (1H, dd, J = 10.2, 5.7 Hz), 3.69
15 (1H, d, J = 13.4 Hz), 3.87 (1H, d, J = 13.4 Hz), 4.23 (1H, dd, J = 7.7, 7.7 Hz), 4.23 (2H, q, J = 7.1 Hz), 4.50 (2H, s), 4.50-4.70 (1H, m), 6.70-6.78 (1H, m), 6.85-7.00 (2H, m), 7.17 (1H, dd, J = 7.7, 7.7 Hz), 7.25-7.45 (6H, m), 7.50-7.68 (4H, m)
APCI-MS m/z : 499 (M+H⁺)

20 (2) Ethyl 3-[(2R, 4R)-2-(4,5-diphenyloxazol-2-yl)-4-methoxypyrrolidin-1-yl]methyl]phenoxyacetate
IR (neat) : 3057, 2979, 2929, 2819, 1759, 1601, 1589, 1487, 1444, 1377 cm⁻¹
NMR (CDCl₃, δ) : 1.27 (3H, t, J = 7.1 Hz), 2.28-2.68 (3H, m), 3.16-3.27
25 (1H, m), 3.33 (3H, s), 3.57 (1H, d, J = 13.4 Hz), 3.79 (1H, dd, J = 8.3, 8.3 Hz), 3.91 (1H, d, J = 13.4 Hz), 3.90-4.05 (1H, m), 4.23 (2H, q, J = 7.1 Hz), 4.49 (2H, s), 6.67-6.77 (1H, m), 6.88-7.02 (2H, m), 7.17 (1H, dd, J = 7.9, 7.9 Hz), 7.22-7.41 (6H, m), 7.52-7.68 (4H, m)
APCI-MS m/z : 513 (M+H⁺)

30 (3) Ethyl 3-[(2R, 4S)-2-(4,5-diphenyloxazol-2-yl)-4-methoxypyrrolidin-1-yl]methyl]phenoxyacetate
IR (neat) : 3059, 2981, 2931, 2821, 1759, 1601, 1589, 1487, 1444, 1375 cm⁻¹
35 NMR (CDCl₃, δ) : 1.27 (3H, t, J = 7.1 Hz), 2.20-2.36 (1H, m), 2.40-2.58

(2H, m), 3.31 (3H, s), 3.46 (1H, dd, $J = 10.1, 6.1$ Hz), 3.63 (1H, d, $J = 13.3$ Hz), 3.90 (1H, d, $J = 13.3$ Hz), 4.00-4.18 (2H, m), 4.23 (2H, q, $J = 7.1$ Hz), 4.48 (2H, s), 6.67-6.76 (1H, m), 6.85-6.97 (2H, m), 7.17 (1H, dd, $J = 7.8, 7.8$ Hz), 7.25-7.43 (6H, m), 7.50-7.67 (4H, m)

5 APCI-MS m/z : 513 ($M+H^+$)

Example 3

To a solution of ethyl 3-[(2R, 4R)-2-(4,5-diphenyloxazol-2-yl)-4-hydroxypyrrolidin-1-yl]methyl]phenoxyacetate (353 mg) in MeOH:1,4-dioxane
10 (1:1, 10 mL) was added 1N NaOH solution (0.744 mL) at 5°C, and the mixture was stirred at room temperature for 4 hours. The reaction mixture was evaporated and Et₂O was added thereto. The resulting solid was collected by filtration to give sodium 3-[(2R, 4R)-2-(4,5-diphenyloxazol-2-yl)-4-hydroxypyrrolidin-1-ylmethyl]phenoxyacetate (327.7 mg).

15 IR (KBr) : 3381, 3057, 2947, 2802, 1608, 1487, 1423, 1338 cm⁻¹

NMR (DMSO-d₆, δ) : 2.00-2.20 (1H, m), 2.47-2.67 (2H, m), 2.82-2.98 (1H, m), 3.40 (1H, d, $J = 14.8$ Hz), 3.73-3.93 (2H, m), 4.03 (2H, s), 4.20-4.38 (1H, m), 4.98 (1H, br), 6.58-6.68 (1H, m), 6.70-6.83 (2H, m), 7.09 (1H, dd, $J = 7.9, 7.9$ Hz), 7.30-7.63 (10H, m)

20 ESI-MS m/z : 493 ($M+H^+$)

Example 4

The following compounds (1) to (4) were obtained according to the similar manner to that of Example 3.

25

(1) Sodium 3-[(2R)-2-(4,5-diphenyloxazol-2-yl)-4-oxopyrrolidin-1-yl]methyl]phenoxyacetate

IR (KBr) : 3379, 3057, 2924, 1761, 1606, 1487, 1423, 1336, 1261 cm⁻¹

30 NMR (DMSO-d₆, δ) : 2.72-3.00 (2H, m), 3.07 (1H, d, $J = 17.6$ Hz), 3.29 (1H, d, $J = 17.6$ Hz), 3.67 (1H, d, $J = 13.3$ Hz), 3.82 (1H, d, $J = 13.3$ Hz), 4.03 (2H, s), 4.50 (1H, dd, $J = 7.1, 7.1$ Hz), 6.57-6.85 (3H, m), 7.02-7.17 (1H, m), 7.20-7.65 (10H, m)

ESI-MS m/z : 491 ($M+H^+$)

35 (2) Sodium 3-[(2R, 4S)-2-(4,5-diphenyloxazol-2-yl)-4-hydroxypyrrolidin-1-

yl)methyl}phenoxyacetate

IR (KBr): 3384, 3059, 2835, 1603, 1489, 1425, 1338, 1261 cm^{-1}

NMR (DMSO- d_6 , δ): 1.97-2.13 (1H, m), 2.25-2.47 (2H, m), 3.24 (1H, dd, J = 9.8, 5.9 Hz), 3.55 (1H, d, J = 13.3 Hz), 3.80 (1H, d, J = 13.3 Hz), 4.02 (2H, s), 4.00-4.13 (1H, m), 4.30-4.43 (1H, m), 6.57-6.68 (1H, m), 6.68-6.82 (2H, m), 7.08 (1H, dd, J = 7.9, 7.9 Hz), 7.30-7.62 (10H, m)

ESI-MS m/z : 493 ($M+H^+$)

(3) Sodium 3-{[(2R, 4R)-2-(4,5-diphenyloxazol-2-yl)-4-methoxypyrrolidin-1-yl)methyl}phenoxyacetate

IR (KBr): 3421, 3059, 2927, 2821, 1606, 1489, 1425, 1336, 1261 cm^{-1}

NMR (DMSO- d_6 , δ): 2.08-2.26 (1H, m), 2.40-2.70 (2H, m), 2.97-3.10 (1H, m), 3.19 (3H, s), 3.43 (1H, d, J = 12.7 Hz), 3.70-3.90 (2H, m), 3.90-4.10 (1H, m), 4.01 (2H, s), 6.55-6.68 (1H, m), 6.68-6.83 (2H, m), 7.09 (1H, dd, J = 8.1, 8.1 Hz), 7.30-7.63 (10H, m)

ESI-MS m/z : 507 ($M+H^+$)

(4) Sodium 3-{[(2R, 4S)-2-(4,5-diphenyloxazol-2-yl)-4-methoxypyrrolidin-1-yl)methyl}phenoxyacetate

IR (KBr): 3384, 3057, 2925, 2821, 1606, 1489, 1425, 1338, 1261 cm^{-1}

NMR (DMSO- d_6 , δ): 2.12-2.55 (3H, m), 3.22 (3H, s), 3.18-3.42 (1H, m), 3.54 (1H, d, J = 13.3 Hz), 3.79 (1H, d, J = 13.3 Hz), 3.95-4.17 (2H, m), 4.02 (2H, s), 6.57-6.70 (1H, m), 6.70-6.85 (2H, m), 7.09 (1H, dd, J = 8.0, 8.0 Hz), 7.30-7.60 (10H, m)

ESI-MS m/z : 507 ($M+H^+$)Example 5

To a solution of oxalyl chloride (0.050 mL) in CH_2Cl_2 (10 mL) was added a solution of DMSO (0.061 mL) in CH_2Cl_2 (0.5 mL) keeping the temperature below -55°C , and stirred for 30 minutes. To the mixture was added a solution of ethyl 3-{[(2R, 4R)-2-(4,5-diphenyloxazol-2-yl)-4-hydroxypyrrolidin-1-yl)methyl}phenoxyacetate (238 mg) in CH_2Cl_2 (3 mL) at the same temperature, then stirred for 1 hour. To the reaction mixture was added triethylamine (0.27 mL), and warmed to room temperature over 30 minutes. After stirring at the same temperature for 30 minutes, the mixture was

diluted with EtOAc, washed with water, saturated sodium hydrogen

carbonate, water and brine, dried (MgSO_4), evaporated. The residue was purified by silica gel column chromatography (hexane-EtOAc 2:1) to give ethyl 3-([(2R)-2-(4,5-diphenyloxazol-2-yl)-4-oxopyrrolidin-1-

5 yl)methyl]phenoxyacetate (191.8 mg).

IR (neat): 3059, 2981, 2931, 2802, 1761, 1603, 1591, 1487, 1446, 1205 cm^{-1}

NMR (CDCl_3 , δ): 1.27 (3H, t, $J = 7.1$ Hz), 2.77-3.05 (2H, m), 3.03 (1H, d, $J = 17.2$ Hz), 3.48 (1H, d, $J = 17.2$ Hz), 3.73 (1H, d, $J = 13.4$ Hz), 3.92
10 (1H, d, $J = 13.4$ Hz), 4.24 (2H, q, $J = 7.1$ Hz), 4.42 (1H, dd, $J = 7.3, 7.3$ Hz), 4.53 (2H, s), 6.72-6.82 (1H, m), 6.88-6.99 (2H, m), 7.15-7.45 (7H, m), 7.50-7.70 (4H, m)

APCI-MS m/z : 497 ($\text{M}+\text{H}^+$)

15 Example 6

To a solution of Ethyl 3-([(2R, 4S)-2-(4,5-diphenyloxazol-2-yl)-4-methoxypyrrolidin-1-yl)methyl]phenoxyacetate (3.00 g) in EtOH (30 mL) was added 1N NaOH solution (6.00 mL) at 5°C, and the mixture was stirred at room temperature for 1 hour. To the reaction mixture was added 1N HCl
20 (6.00 mL) at 5°C and evaporated. The residue was extracted with EtOAc, washed with water and brine, dried (Na_2SO_4), and evaporated in vacuo to give 3-([(2R, 4S)-2-(4,5-diphenyloxazol-2-yl)-4-methoxypyrrolidin-1-yl)methyl]phenoxyacetic acid (2.75 g).

IR (KBr): 3433, 3057, 2931, 2823, 1736, 1591, 1487, 1444, 1225 cm^{-1}

25 NMR ($\text{DMSO}-d_6$, δ): 2.13-2.30 (1H, m), 2.30-2.55 (2H, m), 3.22 (3H, s), 3.20-3.35 (1H, m), 3.60 (1H, d, $J = 13.5$ Hz), 3.80 (1, d, $J = 13.5$ Hz), 3.95-4.18 (2H, m), 4.54 (2H, s), 6.68-6.78 (1H, m), 6.81-6.93 (2H, m), 7.16 (1H, dd, $J = 7.8, 7.8$ Hz), 7.32-7.62 (10H, m)

ESI-MS m/z : 485 ($\text{M}+\text{H}^+$)

30

Example 7

To a solution of 3-([(2R, 4S)-2-(4,5-diphenyloxazol-2-yl)-4-methoxypyrrolidin-1-yl)methyl]phenoxyacetic acid (100 mg) in EtOH (0.65 mL) was added a solution of L-(+)-tartaric acid (32 mg) in EtOH (1.3 mL) at
35 room temperature. To the mixture was added n-hexane (3.9 mL), and the

mixture was stirred at room temperature for 2 hours. The resulting precipitate was collected and dried under reduced pressure to give 3- $\{[(2R, 4S)-2-(4,5-diphenyloxazol-2-yl)-4-methoxypyrrolidin-1-yl]methyl\}$ phenoxyacetic acid tartrate (a L-(+)-tartaric acid addition salt of 3-
5 $\{[(2R, 4S)-2-(4,5-diphenyloxazol-2-yl)-4-methoxypyrrolidin-1-yl]methyl\}$ phenoxyacetic acid) (102 mg).

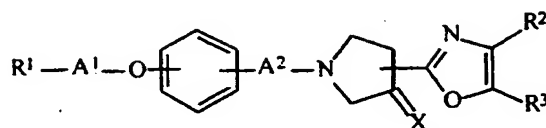
IR (KBr) : 3435, 3028, 2924, 2854, 1722, 1604, 1448, 1412 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.12-2.30 (1H, m), 2.30-2.55 (2H, m), 3.22 (3H, s), 3.20-
3.35 (1H, m), 3.61 (1H, d, $J = 13.6$ Hz), 3.80 (1, d, $J = 13.6$ Hz), 3.95-
10 4.18 (2H, m), 4.30 (2H, s), 4.54 (2H, s), 6.68-6.78 (1H, m), 6.82-6.94
(2H, m), 7.16 (1H, dd, $J = 7.8, 7.8$ Hz), 7.30-7.60 (10H, m)

CLAIMS

1. A compound of the formula:

5



wherein

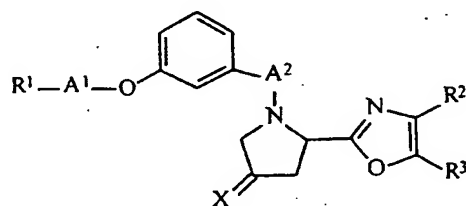
- 10 R^1 is carboxy or protected carboxy,
 R^2 is aryl which may have substituent(s),
 R^3 is aryl which may have substituent(s),
 X is oxygen or a pair of hydrogen and R^5 (wherein R^5 is hydroxy or protected hydroxy), and
 15 A^1 and A^2 are each independently lower alkylene and prodrug thereof, and its salt.

2. A compound of claim 1, wherein

- R^1 is carboxy or esterified carboxy,
 20 R^2 is phenyl or lower alkylphenyl,
 R^3 is phenyl or lower alkylphenyl, and
 X is oxygen or a pair of hydrogen and R^5 (wherein R^5 is hydroxy or lower alkoxy).

25 3. A compound of claim 2, which is a compound of the formula:

30



wherein

- R^1 is carboxy or lower alkoxy carbonyl,
 R^2 is phenyl or lower alkylphenyl,
 35 R^3 is phenyl or lower alkylphenyl, and

X is oxygen or a pair of hydrogen and R⁵ (wherein R⁵ is hydroxy or lower alkoxy).

A¹ and A² are each independently lower alkylene

- 5 4. A compound of claim 3, wherein
R¹ is carboxy, or ethoxycarbonyl,
R² is phenyl,
R³ is phenyl,
X is oxygen or a pair of hydrogen and R⁵ (wherein R⁵ is hydroxy or
10 methoxy), and
A¹ and A² is each methylene.
5. A compound according to claim 1, which is a compound selected from the group consisting of
- 15 (1) ethyl 3-[(2R, 4R)-2-(4,5-diphenyloxazol-2-yl)-4-hydroxypyrrolidin-1-yl]methyl}phenoxyacetate,
(2) ethyl 3-[(2R, 4S)-2-(4,5-diphenyloxazol-2-yl)-4-hydroxypyrrolidin-1-yl]methyl}phenoxyacetate,
(3) ethyl 3-[(2R, 4R)-2-(4,5-diphenyloxazol-2-yl)-4-methoxypyrrolidin-1-yl]methyl}phenoxyacetate,
20 (4) ethyl 3-[(2R, 4S)-2-(4,5-diphenyloxazol-2-yl)-4-methoxypyrrolidin-1-yl]methyl}phenoxyacetate,
(5) sodium 3-[(2R, 4R)-2-(4,5-diphenyloxazol-2-yl)-4-hydroxypyrrolidin-1-yl]methyl}phenoxyacetate,
25 (6) Sodium 3-[(2R)-2-(4,5-diphenyloxazol-2-yl)-4-oxopyrrolidin-1-yl]methyl}phenoxyacetate,
(7) sodium 3-[(2R, 4S)-2-(4,5-diphenyloxazol-2-yl)-4-hydroxypyrrolidin-1-yl]methyl}phenoxyacetate,
(8) sodium 3-[(2R, 4R)-2-(4,5-diphenyloxazol-2-yl)-4-methoxypyrrolidin-1-yl]methyl}phenoxyacetate,
30 (9) sodium 3-[(2R, 4S)-2-(4,5-diphenyloxazol-2-yl)-4-methoxypyrrolidin-1-yl]methyl}phenoxyacetate,
(10) ethyl 3-[(2R)-2-(4,5-diphenyloxazol-2-yl)-4-oxopyrrolidin-1-yl]methyl}phenoxyacetate,
35 (11) 3-[(2R, 4S)-2-(4,5-diphenyloxazol-2-yl)-4-methoxypyrrolidin-1-

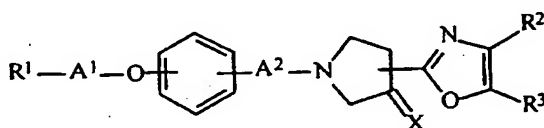
25

yl)methyl}phenoxyacetic acid, and
 (12) 3-[(2R, 4S)-2-(4,5-diphenyloxazol-2-yl)-4-methoxypyrrolidin-1-yl)methyl}phenoxyacetic acid tartrate.

5

6. A process for preparing a compound of the formula:

10

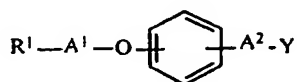


wherein

- R¹ is carboxy or protected carboxy,
 R² is aryl which may have substituent(s),
 R³ is aryl which may have substituent(s),
 15 X is oxygen or a pair of hydrogen and R⁵ (wherein R⁵ is hydroxy or protected hydroxy), and
 A¹ and A² are each independently lower alkylene and prodrug thereof, and its salt,
 which comprises

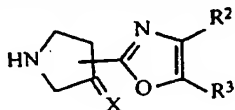
20

(1) reacting a compound of the formula:



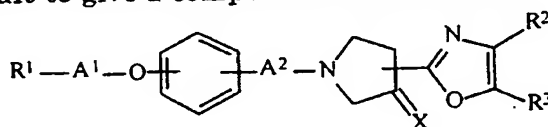
25

or its salt with a compound of the formula:



or its salt to give a compound of the formula:

30



or its salt,

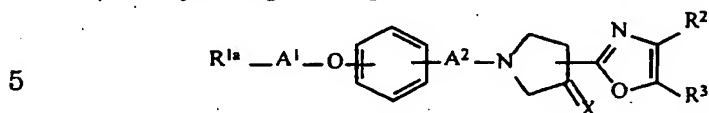
in the above formulas,

35

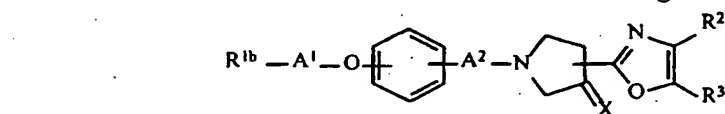
R¹, R², R³, X, A¹ and A² are each as defined above,

Y is leaving group, or

(2) subjecting a compound of the formula:



or its salt to elimination reaction to give a compound of the formula:



or its salt,

in the above formulas,

R², R³, X, A¹ and A² are each as defined above,

R^{1a} is protected carboxy, and

15 R^{1b} is carboxy.

7. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 thereof in admixture with pharmaceutically acceptable carriers.

20

8. A use of a compound of claim 1 as a prostaglandin I₂ agonist.

9. A method for treating or preventing arterial obstruction, restenosis or ischemic complications after coronary angioplasty, arteriosclerosis, cerebrovascular disease, ischemic heart disease, dermatosis, or hepatic insufficiency which comprises administering a compound of claim 1 to human or animals.

25

10. A process for preparing a pharmaceutical composition which comprises admixing a compound of claim 1 with a pharmaceutically acceptable carrier.

30

INTERNATIONAL SEARCH REPORT

Inter. Appl. No.

PCT/JP 00/05453

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D413/04 A61K31/422 A61P9/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | WO 97 03973 A (TABUCHI SEIICHIRO ;TANIGUCHI KIYOSHI (JP); HATTORI KOUJI (JP); OKI) 6 February 1997 (1997-02-06) cited in the application Compound (I-D), examples 10,20,30,31,33,34(5),34(23) ---- | 1-10 |
| A | WO 95 17393 A (TABUCHI SEIICHIRO ;TANIGUCHI KIYOSHI (JP); HATTORI KOUJI (JP); NAG) 29 June 1995 (1995-06-29) cited in the application examples 6,8,17 ---- | 1,7-10 |
| A | WO 99 21843 A (HATTORI KOUJI ;FUJII NAOAKI (JP); TAKAMURA FUJIKO (JP); TANAKA AKI) 6 May 1999 (1999-05-06) examples 9,10,16 ----- | 1,7-10 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

13 November 2000

Date of mailing of the international search report

24/11/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040. Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Seitner, I

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. onal Application No

PCT/JP 00/05453

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| WO 9703973 A | 06-02-1997 | AU 716304 B | 24-02-2000 |
| | | AU 6469796 A | 18-02-1997 |
| | | CN 1196726 A | 21-10-1998 |
| | | EP 0842161 A | 20-05-1998 |
| | | HU 9900881 A | 30-08-1999 |
| | | JP 11509191 T | 17-08-1999 |
| | | US 5972965 A | 26-10-1999 |
| WO 9517393 A | 29-06-1995 | AT 194335 T | 15-07-2000 |
| | | AU 686286 B | 05-02-1998 |
| | | AU 1200695 A | 10-07-1995 |
| | | CA 2179399 A | 29-06-1995 |
| | | CN 1138328 A,B | 18-12-1996 |
| | | CN 1229795 A | 29-09-1999 |
| | | DE 69425162 D | 10-08-2000 |
| | | EP 0736018 A | 09-10-1996 |
| | | ES 2147836 T | 01-10-2000 |
| | | HU 76341 A | 28-08-1997 |
| | | JP 9506894 T | 08-07-1997 |
| | | US 6025375 A | 15-02-2000 |
| WO 9921843 A | 06-05-1999 | AU 9282398 A | 17-05-1999 |
| | | BR 9813281 A | 22-08-2000 |
| | | EP 1027340 A | 16-08-2000 |